Clinical Laboratory Improvement Advisory Committee

FDA White Oak Campus

Tuesday, April 10, 2018

Implementation of Next-Generation Sequencing in Clinical and Public Health Laboratories

Background/Introduction

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Geneticist

Quality and Safety Systems Branch

Implementation of Next Generation Sequencing in Clinical Laboratories

• Background / Introduction	Ira M. Lubin, PhD, FACMG
• Public Health Perspective	Rebecca Hutchins, MS, MBA
• Clinical Laboratory Perspective	John D. Pfeifer, MD, PhD
• CLIAC Discussion	

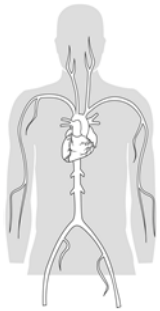
Background / Introduction

- Next-generation sequencing in clinical and public health applications
- Integrating next-generation sequencing into clinical laboratory testing
- Practice and regulatory framework for assuring the quality of clinical next-generation sequencing
- Proposed CLIAC Workgroup
- Questions for CLIAC

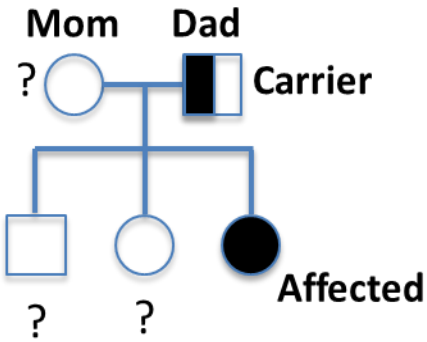
Next-Generation Sequencing in Clinical and Public Health Applications

Pediatrics:

- Rare Disease
- Developmental Disabilities

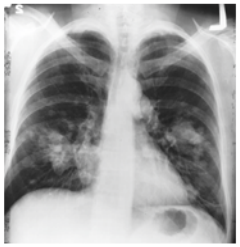


Chronic Disease



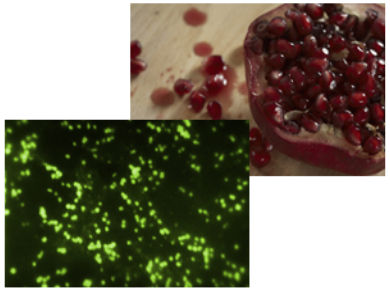
Screening:

- Carrier Screening



Cancer

Transplant



Pathogens:

- Identification
- Outbreak response
- Antibiotic resistance

What is the Landscape of Next-Generation Sequencing Offerings in the United States?

New York Clinical Laboratory Evaluation Program
https://www.wadsworth.org/regulatory/clep/approved-ldt

81 Laboratories
(searched 3/23/2018)

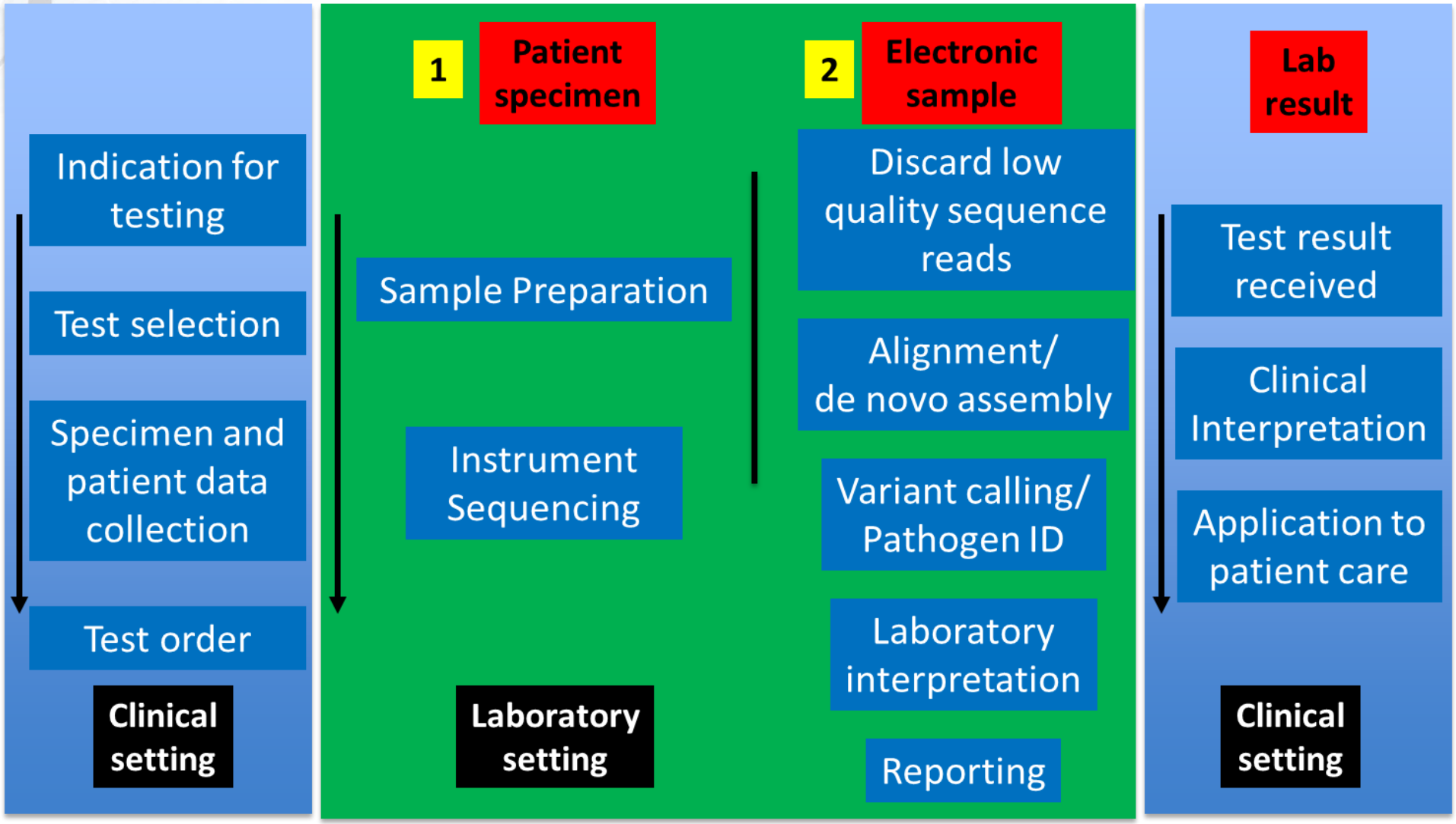
College of American Pathologists Accreditation Data (per organizational contact)

331 laboratories
(provided 3/16/2018)

Genetic Testing Registry
https://www.ncbi.nlm.nih.gov/gtr/

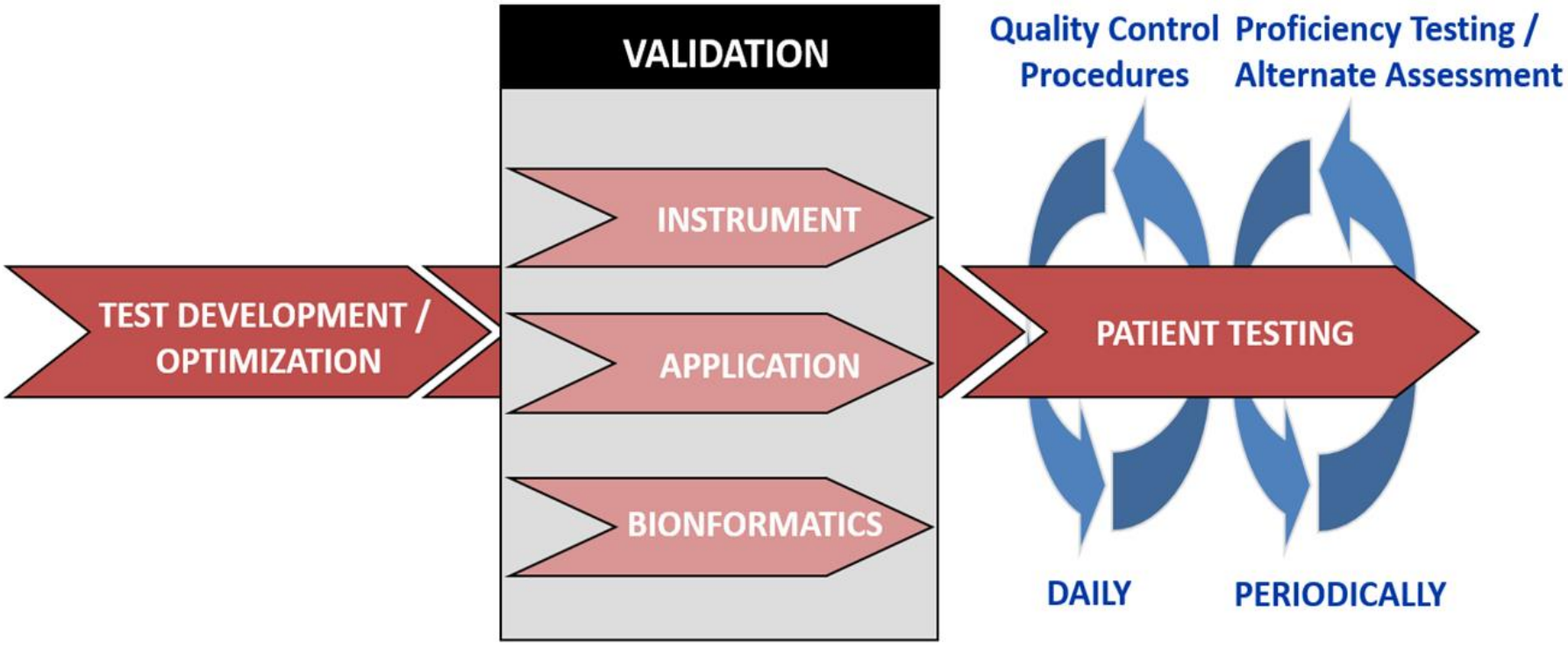
80 Laboratories
(Provided 3/12/2018)

Workflow: Next Generation Sequencing



Framework for the Implementation of Clinical NGS Testing

As of 2018, the majority of clinical NGS tests are developed within the laboratory that they are offered.



Gargis et al., Nat Biotechnol. 2012;30:1033

Practice and Regulatory Framework for Assuring the Quality of Clinical Next-Generation Sequencing

Applying the CLIA regulations to clinical next-generation sequencing is challenging due to the novelty and complexity of the technology, and new paradigms for data analyses

- **Code of Federal Regulations**. **The Clinical Laboratory Improvement Amendments (CLIA).** 42 CFR Part 493 sec. 1256.
- **Interpretive guidelines***:* *https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/som107ap_c_lab.pdf*

Applying CLIA to Next-Generation Sequencing in the Clinical Setting

- Test validation *(CLIA general requirements at §493.1253)*
- Quality control procedures *(CLIA general requirements at §493.1256; unidirectional workflow for molecular amplification at §493.1101 (a)(3))*
  - Quality control materials (physical and electronic)?
  - Use of external data to support analyses?
- Test ordering *(CLIA general requirements at §493.1241)*
- Result Reporting *(CLIA general requirements at §493.1291)*
- Proficiency testing *(CLIA does not specify PT requirements for NGS, so alternative performance assessment requirements at §493.1236(c) apply)*
- Personnel competencies (Subpart M; No specific requirements)
- Bioinformatics pipeline quality assessment (No specific requirements)

Other issues:

- Distributive testing – single test / multiple sites
- Reporting of secondary findings
- Reanalysis

Next Generation Sequencing: Standardization of Clinical Testing

Assuring the quality of next-generation sequencing in clinical laboratory practice

To the Editor:

We direct your readers' attention to the principles and guidelines (**Supplementary Guidelines**) developed by the Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) workgroup. These guidelines represent initial steps to ensure that results from tests based on next-generation sequencing (NGS) are reliable and useful for clinical decision making. The US Centers for Disease Control and Prevention (CDC) convened this national workgroup, which collaborated to define platform-independent approaches for establishing technical process elements of a quality management system (QMS) to assure the analytical validity and compliance of NGS tests with existing regulatory and professional quality standards. The workgroup identified and addressed gaps in

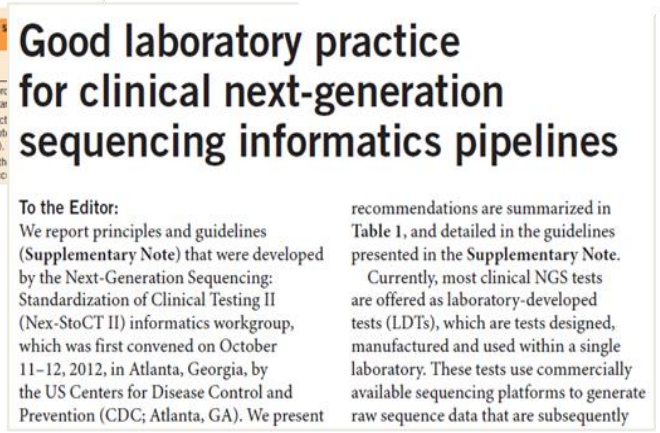
The workgroup recommendations are summarized in **Table 1**. Although the workgroup focused on detection of DNA sequence variations associated with heritable human disorders, many of the principles and recommendations described are also relevant to the application of NGS to other areas of laboratory medicine, including the diagnosis, prognosis and treatment of cancer and infectious-disease testing.

Validation is the process of establishing analytical performance specifications for a clinical test system developed in house to confirm that the system is suitable for its intended use[1]. During the validation process, the laboratory must demonstrate that the assay functions as expected and provides

Table 1 Selected workgroup recommendations for establishing NGS test s clinical use

Requirements for test establishment	Objective	NGS-specific recommendations[a]
Validation	Document reliability of the platform, test, and informatics pipeline before testing of patient specimens	•Platform validation: establish that the system pro sequence analysis across the genomic regions ta •Test validation: establish that the system correct disease-associated (and other) variants in target genome (**Supplementary Guidelines**, section 4). •Informatics pipeline validation: establish that th reliably analyze platform data to produce an acc

Gargis et. al. Nat. Biotechnol. 2012; 30:1033-1036+ Supplemental



Good laboratory practice for clinical next-generation sequencing informatics pipelines

To the Editor:

We report principles and guidelines (**Supplementary Note**) that were developed by the Next-Generation Sequencing: Standardization of Clinical Testing II (Nex-StoCT II) informatics workgroup, which was first convened on October 11–12, 2012, in Atlanta, Georgia, by the US Centers for Disease Control and Prevention (CDC; Atlanta, GA). We present recommendations are summarized in **Table 1**, and detailed in the guidelines presented in the **Supplementary Note**.

Currently, most clinical NGS tests are offered as laboratory-developed tests (LDTs), which are tests designed, manufactured and used within a single laboratory. These tests use commercially available sequencing platforms to generate raw sequence data that are subsequently

Gargis et al. Nat. Biotechnol. 2015;33: 689-693 + Supplemental

Principles and Recommendations for Standardizing the Use of the Next-Generation Sequencing Variant File in Clinical Settings

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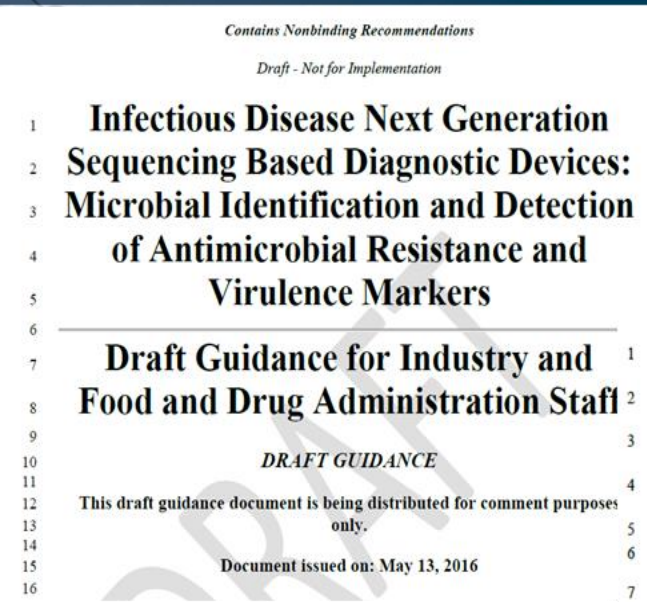
Lubin IM et al. J Mol Diagn. 2017;19:417-426

CDC facilitated the development of the first consensus guideline for clinical next-generation sequencing.

The Food and Drug Administration: Draft Guidance for Next-Generation Sequencing



Contains Nonbinding Recommendations

Draft - Not for Implementation

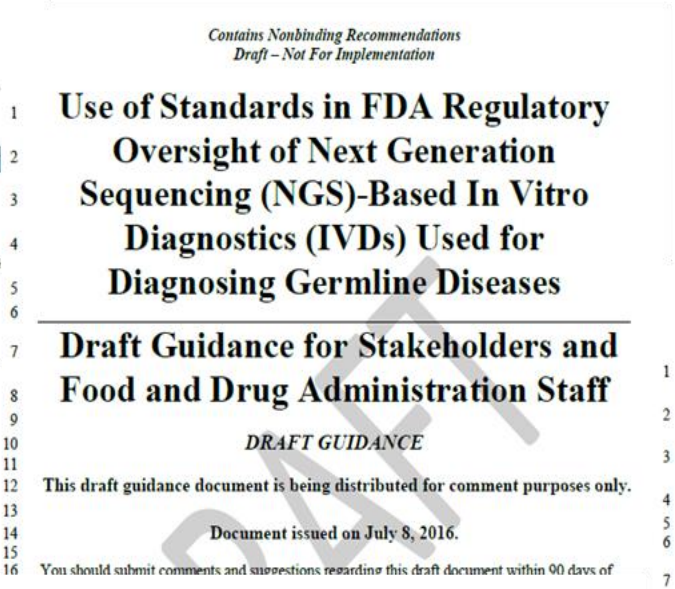
Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on: May 13, 2016



Contains Nonbinding Recommendations
Draft – Not For Implementation

Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases

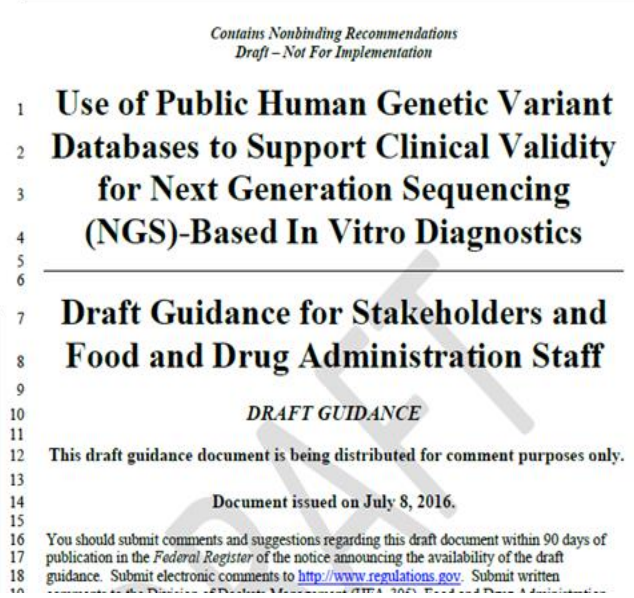
Draft Guidance for Stakeholders and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 8, 2016.

You should submit comments and suggestions regarding this draft document within 90 days of



Contains Nonbinding Recommendations
Draft – Not For Implementation

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics

Draft Guidance for Stakeholders and Food and Drug Administration Staff

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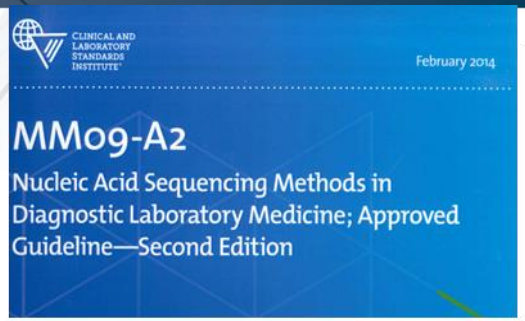
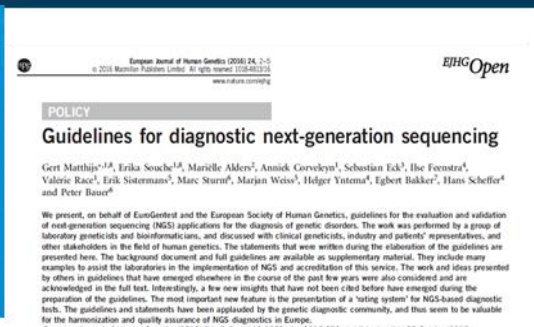
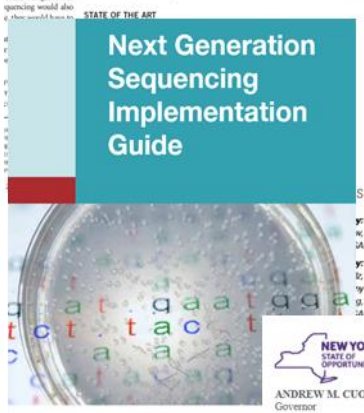
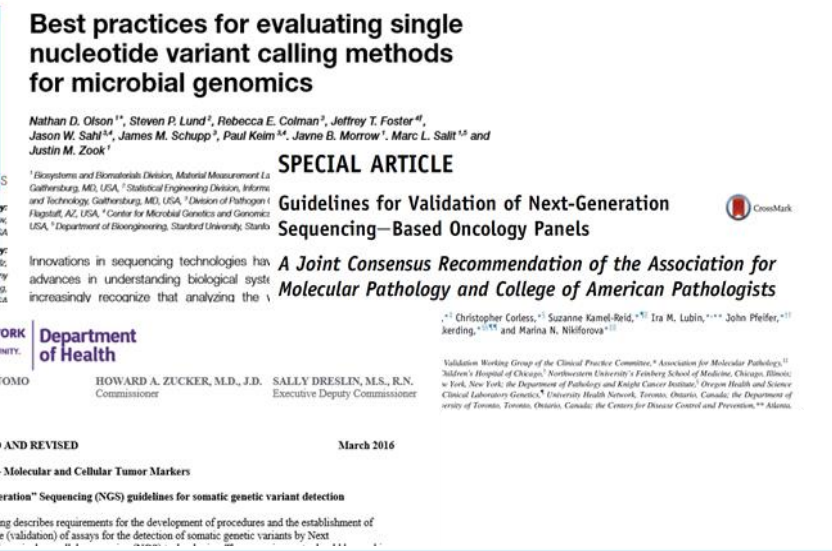
A Sampling of Professional Guidance









Summary

- **Next generation sequencing is continuing to integrate into diverse medical disciplines.**
- **Bioinformatics (computational analysis) comprises a significant component of the test.**
- **Communication between the laboratory professional (s) and clinician(s) is vital toward understanding of the available testing, limitations, and test findings**
- **Clinical NGS testing is covered under CLIA but application of the laboratory requirements may not be sufficiently defined.**

Proposed CLIAC NGS Workgroup

Proposed Charge

Provide input to CLIAC for consideration in developing recommendations to CDC, CMS, and FDA for assuring the quality of next generation sequencing in clinical laboratory settings

Proposed Workgroup Tasks

- **Identify challenges in applying the existing regulatory framework**
- **Identify challenges and gaps in guidance**
- **Consider and suggest strategies to address the identified gaps and challenges**
- **Consider and suggest strategies for assuring workforce competency**

Questions for CLIAC

1. What major gaps and issues do laboratories experience when implementing NGS-based testing for various applications?

2. What guidance is lacking for laboratories that perform NGS testing to address critical steps in the total testing process?

3. How can CDC, CMS, and FDA assist in filling NGS-related gaps and providing guidance to laboratories?

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For more information please contact Centers for Disease Control and Prevention

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E-mail: cdcinfo@cdc.gov | Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.